Challenges and unrealised potential of clinical research

Peter M Rothwell
Action Research Professor of Neurology
University of Oxford

AJS MacFadzean Lecture, 19 Nov 2017
Medical Student 1936

Prof McFadzean and Dr Rosie Young at his retirement party, ca 1974
Group photo: farewell party for Dr and Mrs CC Wong, Kum Ling Restaurant prior to their departure for the UK, ca 1952
Back row (from left): Drs J Pan, ST Hiew, Gerald Choa, Olaf Skinsnes, CT Huang, Profs AJS McFadzean and PC Hou, Drs Stephen Chang, KH Chau, Ramon Ruiz, SS Leung, TW Wu, ---, Mr Yung (chief technologist in pathology)
Front row (from left): Dr HC Kwaan, Mrs CT Huang, ---, Mrs PC Hou, Mrs CC Wong, Dr CC Wong, Mrs McFadzean, Miss Glen Mitchell (Nursing Sister, UMU), Dr Irene Osmund, ---, Dr D Todd

Figure 1: Number of chronic disorders by age-group
Medical research pathway

Basic laboratory science
Clinical laboratory science
“Translational research”
Cohort studies
Randomized trials
Population studies
Clinical practice
<table>
<thead>
<tr>
<th>Research activity</th>
<th>MRC</th>
<th>WT</th>
<th>BHF</th>
<th>CRUK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underpinning †,*</td>
<td>41.2</td>
<td>49.2</td>
<td>27.5</td>
<td>24.3</td>
</tr>
<tr>
<td>Aetiology *</td>
<td>38.5</td>
<td>40.5</td>
<td>48.8</td>
<td>35.2</td>
</tr>
<tr>
<td>Prevention</td>
<td>2.9</td>
<td>1.9</td>
<td>1.8</td>
<td>2.1</td>
</tr>
<tr>
<td>Detection &amp; diagnosis</td>
<td>4.5</td>
<td>1.7</td>
<td>6.0</td>
<td>6.1</td>
</tr>
<tr>
<td>Treatment development *</td>
<td>5.6</td>
<td>4.3</td>
<td>9.3</td>
<td>17.3</td>
</tr>
<tr>
<td>Treatment evaluation</td>
<td>4.5</td>
<td>1.7</td>
<td>5.2</td>
<td>11.7</td>
</tr>
<tr>
<td>Disease management</td>
<td>1.2</td>
<td>0.2</td>
<td>0.8</td>
<td>2.9</td>
</tr>
<tr>
<td>Health services</td>
<td>1.6</td>
<td>0.5</td>
<td>0.6</td>
<td>0.4</td>
</tr>
</tbody>
</table>

† Research aimed at understanding normal biological functioning  * Laboratory-based

Rothwell PM. Funding for practice-oriented clinical research. *Lancet* 2006; 368: 262-6

Rothwell PM. Medical academia is failing patients and clinicians. *BMJ* 2006; 332:863-4
## Spectrum of medical research

<table>
<thead>
<tr>
<th>Clinical innovation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical effectiveness</td>
</tr>
<tr>
<td>Clinical exploration</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Basic laboratory science</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Translational research&quot;</td>
</tr>
<tr>
<td>Cohort studies</td>
</tr>
<tr>
<td>Randomized trials</td>
</tr>
<tr>
<td>Population studies</td>
</tr>
<tr>
<td>Clinical practice</td>
</tr>
</tbody>
</table>
# Cataract Surgery

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Percentage With Cataracts</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-54</td>
<td>5.2%</td>
</tr>
<tr>
<td>55-59</td>
<td>9.1%</td>
</tr>
<tr>
<td>60-64</td>
<td>15.4%</td>
</tr>
<tr>
<td>65-69</td>
<td>24.7%</td>
</tr>
<tr>
<td>70-74</td>
<td>36.5%</td>
</tr>
<tr>
<td>75-79</td>
<td>49.5%</td>
</tr>
<tr>
<td>80+</td>
<td>68.3%</td>
</tr>
</tbody>
</table>

Source: National Eye Institute (NEI), U.S. National Institutes of Health
Joint replacement surgery
The durability of endovascular coiling versus neurosurgical clipping of ruptured cerebral aneurysms: 18 year follow-up of the UK cohort of the International Subarachnoid Aneurysm Trial (ISAT)

Andrew J. Molyneux, Jacqueline Birks, Alison Clarke, Mary Sneade, Richard S C Kerr

Figure 2: Kaplan-Meier plot of cumulative mortality
Patients observed for 10–18.5 years in 22 UK centres.

Lancet 2015; 385: 691-97
Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial

Wendy S Atkin, Rob Edwards, Ines Kralj-Hans, Kate Wooldrage, Andrew R Hart, John M A Northover, D Max Parkin, Jane Wardle, Stephen W Duffy, Jack Cuzick, UK Flexible Sigmoidoscopy Trial Investigators

Distal colorectal cancer

Colorectal cancer deaths
Spectrum of medical research

Clinical innovation
Clinical effectiveness
Clinical exploration

Basic laboratory science
“Translational research”
Cohort studies
Randomized trials
Population studies
Clinical practice
Neuroprotection in acute ischaemic stroke

Experimental approaches

More than 1000 compounds tested in animal studies and clinical trials
UK stroke research funding - 1998

- MRC - only 1 of 238 new grants was for stroke
  - 3 ongoing RCTs in stroke vs 65 in cancer
- Wellcome Trust - £123,000 (0.03%) spent on stroke research out of a total spend of £392.6 million.

Trials of mechanical thrombectomy in patients with acute ischaemic stroke

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>MT (+/- IVT)</th>
<th>IVT</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Berkhemar et al 2014</td>
<td>76</td>
<td>233</td>
<td>51</td>
<td>267</td>
</tr>
<tr>
<td>Campbell et al 2015</td>
<td>25</td>
<td>35</td>
<td>14</td>
<td>35</td>
</tr>
<tr>
<td>Goyal et al 2015</td>
<td>87</td>
<td>164</td>
<td>43</td>
<td>147</td>
</tr>
<tr>
<td>Jovin et al 2015</td>
<td>45</td>
<td>103</td>
<td>29</td>
<td>103</td>
</tr>
<tr>
<td>Saver et al 2015</td>
<td>59</td>
<td>98</td>
<td>33</td>
<td>93</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>633</td>
<td>454</td>
<td>645</td>
<td>454</td>
</tr>
</tbody>
</table>

Total events: 292 (MT (+/- IVT)) 170 (IVT)

Heterogeneity: Chi² = 2.26, df = 4 (P = 0.69); I² = 0%
Test for overall effect: Z = 7.13 (P < 0.00001)
Hemicraniectomy in major hemispheric stroke

41 year old man with ischaemic stroke due to a right carotid dissection

[Images of brain scans labeled A, B, and C with timeframes: 6-hours, 24-hours, 5-days]
## Hemicraniectomy vs conservative Rx

### Outcome / Patients

<table>
<thead>
<tr>
<th></th>
<th>Conservative</th>
<th>Surgery</th>
<th>ARR (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DECIMAL</td>
<td>14 / 18</td>
<td>5 / 20</td>
<td>52.8</td>
<td>25.8-79.8</td>
</tr>
<tr>
<td>DESTINY</td>
<td>10 / 15</td>
<td>4 / 17</td>
<td>43.1</td>
<td>11.9-74.4</td>
</tr>
<tr>
<td>HAMLET</td>
<td>8 / 9</td>
<td>4 / 14</td>
<td>60.3</td>
<td>29.0-91.6</td>
</tr>
<tr>
<td>TOTAL</td>
<td>32 / 42</td>
<td>13 / 51</td>
<td>51.2</td>
<td>33.9-68.5</td>
</tr>
</tbody>
</table>

Significance p < 0.0001  
Heterogeneity p = 0.74

### mRS >4 at 12 months

#### Modified Rankin Scores at 12 months follow up

Conservative

<table>
<thead>
<tr>
<th>Score</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>2.5% (1/42)</td>
</tr>
<tr>
<td>3</td>
<td>19% (8/42)</td>
</tr>
<tr>
<td>4</td>
<td>2.5% (1/42)</td>
</tr>
<tr>
<td>5</td>
<td>5% (2/42)</td>
</tr>
<tr>
<td>5</td>
<td>71% (30/42)</td>
</tr>
</tbody>
</table>

Surgery

<table>
<thead>
<tr>
<th>Score</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>14% (7/51)</td>
</tr>
<tr>
<td>3</td>
<td>29% (15/51)</td>
</tr>
<tr>
<td>4</td>
<td>31% (16/51)</td>
</tr>
<tr>
<td>5</td>
<td>4% (2/51)</td>
</tr>
<tr>
<td>5</td>
<td>22% (11/51)</td>
</tr>
</tbody>
</table>

Trials of closure of patent foramen ovale in young patients with cryptogenic stroke

Kaplan–Meier Cumulative Estimates of Probability of Stroke in the PFO Closure Group versus the Antiplatelet-Only Group.

Probability of Freedom from Clinical Evidence of Recurrent Ischemic Stroke.


### Association of PFO and cryptogenic stroke by age (<60) in the Oxford Vascular Study

<table>
<thead>
<tr>
<th></th>
<th>Cryptogenic n/total (%)</th>
<th>Known aetiology n/total (%)</th>
<th>OR (95%CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any right-to-left shunt</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤60</td>
<td>29/76 (38.2)</td>
<td>16/50 (32.0)</td>
<td>1.31 (0.62-2.79)</td>
<td>0.48</td>
</tr>
<tr>
<td>&gt;60</td>
<td>70/194 (36.1)</td>
<td>42/202 (20.8)</td>
<td>2.15 (1.37-3.37)</td>
<td>0.001</td>
</tr>
<tr>
<td>Total</td>
<td>99/270 (36.7)</td>
<td>58/252 (23.0)</td>
<td>1.94 (1.32-2.84)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Large right-to-left shunt</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤60</td>
<td>16/76 (21.1)</td>
<td>12/50 (24.0)</td>
<td>0.84 (0.36-1.98)</td>
<td>0.70</td>
</tr>
<tr>
<td>&gt;60</td>
<td>25/194 (12.9)</td>
<td>15/202 (7.4)</td>
<td>1.84 (0.94-3.62)</td>
<td>0.07</td>
</tr>
<tr>
<td>Total</td>
<td>41/270 (15.2)</td>
<td>27/252 (10.7)</td>
<td>1.49 (0.89-2.51)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Unpublished data
Spectrum of medical research

Clinical innovation
Clinical effectiveness
Clinical exploration

Basic laboratory science
"Translational research"
Cohort studies
Randomized trials
Population studies
Clinical practice
Getting the simple things right

NHS 2017

->1 million patient interactions / day

-£120 billion / year

More effective use of existing preventive strategies by:

• Better prognostication
• Better phenotyping
• Better understanding of known risk factors
• Better understanding of existing treatments

Rothwell PM. Funding for practice-oriented clinical research. Lancet 2006; 368: 262-6

Rothwell PM. Medical academia is failing patients & clinicians. BMJ 2006; 332:863-4
Carotid endarterectomy

Stenosis 70-99% (excluding post-stenotic narrowing)
Ipsilateral Carotid Territory Ischaemic Stroke
Plus Any Surgical Stroke or Surgical Death

Patients
Surgery  573  487  454  427  404  374  315  237  157  86  20
No surgery  498  393  332  299  284  254  218  166  90  36  10

Years from randomisation

Proportion free of event

Log Rank = 30.7
p < 0.00001
Effect of carotid endarterectomy stratified by time from last event to randomisation

Ipsilateral ischaemic stroke and operative stroke or death

<table>
<thead>
<tr>
<th>Weeks between symptomatic event and randomisation</th>
<th>ARR (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2</td>
<td>32.7</td>
<td></td>
</tr>
<tr>
<td>2-4</td>
<td>16.0</td>
<td>13.8</td>
</tr>
<tr>
<td>4-12</td>
<td>11.2</td>
<td>3.4</td>
</tr>
<tr>
<td>12+</td>
<td>9.4</td>
<td>-2.9</td>
</tr>
</tbody>
</table>

ARR: Absolute Risk Reduction

Lancet 2004; 363: 915-24
Risk stratification for endarterectomy for symptomatic carotid stenosis

Risk of ischaemic stroke distal to 50-99% asymptomatic carotid stenosis

**Events**

<table>
<thead>
<tr>
<th>Event</th>
<th>N</th>
<th>FU (person yrs)</th>
<th>Rate (annual risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral Stroke</td>
<td>3*</td>
<td>520</td>
<td>0.58 (0.22 – 1.54)</td>
</tr>
<tr>
<td>Ipsilateral TIA or Stroke</td>
<td>10</td>
<td>511</td>
<td>1.96 (1.05 - 3.64)</td>
</tr>
<tr>
<td>Mortality</td>
<td>48**</td>
<td>524</td>
<td>9.16 (6.90 - 12.15)</td>
</tr>
</tbody>
</table>

* 2 strokes occurred in patients with AF; ** No deaths due stroke ipsilateral stroke
Oxford Vascular Study
Population: 92,000 (cf Framingham: 5209)

- All acute TIA, stroke, ACS, AAA, PVD
  - Phase 1 (2002-2012): >8000 patients
- 9 general practices (100 GPs)
- Acute assessment
  - Detailed phenotyping; blood, DNA
- Regular face-to-face follow-up
  - Cognitive assessments at each visit
- No upper age limit (30% events >80 yrs)
- Electronic record linkage

OXVASC-Cog 1
- 2002-2007
- n=1516
- mainly CT-based

OXVASC-Cog 2
- 2007-2012
- n=1492
- partly MRI-based

OXVASC-Cog 3
- 2012-2017
- n=1500
- MRI & fMRI (AVIC)
- Vascular physiol.

“Fully-phenotyped Cohort”
Brain imaging (MRI; fMRI; PET)
Vascular imaging (MRA; TCD)
Cardiac imaging (Echo)
Cardiac monitoring (R-test)
Vascular physiology
BP monitoring (COMMITT)
Biomakers
Genetics

Acute Vascular Imaging Centre

Cardiovascular physiology

Cerebrovascular physiology
Age- and sex-specific rates per 100,000 population (2002-12) of incident acute abdominal aortic aneurysm (AAA)

155 people had 174 AAA (44% of events missed by routine coding)
- only 22.2% in men aged 65-74

The new UK screening programme for men aged 65 will prevent only 5.6% of all aneurysm-related deaths (121 scans per year of life saved).

Screening only male smokers aged 65 and then all men at age 75 would prevent 21.1% of deaths and 33.3% of life-years lost (34 per year of life saved).

Current screening will prevent only 2.1% of all aneurysm-related deaths by 2030, by which time 91.0% will occur at age ≥75, 61.6% at ≥85 and 28.6% in women.

J Am Heart Assoc 2015; 4. pii: e001926.
Circulation 2015 Sep 8. [Epub ahead of print]
Antiplatelet treatment in secondary prevention of vascular events

- 50% of patients taking antiplatelet drugs are now aged ≥75y
Long-term risk of bleeding
Study design and analysis

All first TIA and ischaemic stroke in OXVASC
(01/04/2002 to 31/03/2012)

Excluded
- Not treated with antiplatelet medication
- New warfarin use

All patients on antiplatelet treatment (n=2072)

Censored
- New warfarin use
- Death
- End of follow-up (31/03/2013)

Bleeds details
(n=254)

Severity (CURE criteria)

Outcome (non-disabling, disabling, fatal)

Lancet 2017; 390: 490-499
Major bleeding events in OXVASC

Disabling or fatal bleeds >75 years:
HR = 7.25 (3.79-13.88), p<0.0001
Early risk of major stroke

Risk of stroke (%)

Days

TIA
Minor stroke

Definite TIAs
All referrals

ABCD System

Stroke 2003; 34: e138-e40
Brain 2003; 126:1940-54
Neurology 2004; 62: 569-74
Stroke 2004; 35:1925-9
BMJ 2004; 328: 326-328
Lancet 2004; 363: 915-24
Neurology 2005; 64: 817-20
Lancet 2005; 366: 29-36
Stroke 2006; 37:320-2
Lancet Neurol 2006; 5: 323-31
Cerebrovasc Dis 2007;24:231-5
Lancet 2007; 369:283-92
Lancet Neurol 2010; 6:1063-72
Neurology 2009; 72:1941-7
Stroke 2010; 41: 667-73
Lancet Neurol 2010: 9:1060-9
Lancet 2010; 366: 29-36
Stroke 2010; 41: 851-6
Lancet Neurol 2010; 9:106-9
Lancet 2011; 377; 1681-92
Neurology 2004; 62: 569-74
Lancet 2004; 363: 915-24
Stroke 2006; 37:320-2
Cerebrovasc Dis 2007;24:231-5
Neurology 2009; 72:1941-7
Stroke 2010; 41:1907-13
The short and long-term risk of stroke after minor stroke, TIA and isolated negative focal neurological symptoms in 3000 patients from the Oxford Vascular Study.

![90-day risk of stroke](chart)

![90-day to 10-year risk of stroke](chart)
Long-term risk of stroke following an episode of transient confusion

Tuna M. et al. ESO 2016.
The 24 hour risk of recurrent stroke after TIA
OXVASC years 1-5

24 hours: **5.2%** (95% CI 3.2-7.2)
(7 days: 9.9%, 7.2-12.5)

Neurology 2009; 72:1941-7
EXPRESS Study

Phase 1: months 1-30
- daily appointment clinic
- advice faxed to GP

Phase 2: months 30-60
- emergency clinic
- treatment given in clinic

- Antiplatelet treatment
  - Aspirin (300mg loading / 75mg daily)
  - Clopidogrel in high-risk cases
    - 300mg load + 75mg daily for 1 month
  - Dipyridamole after 1 month
- Simvastatin 40mg
- Perindopril 4mg + indapamide 1.25mg

90-day risk of recurrent stroke after first seeking medical attention in all patients with TIA or stroke referred to the EXPRESS study clinic.

Lancet 2007; 370:1432-42
Lancet Neurol 2009; 8:235-43
Aspirin after TIA or ischaemic stroke

Antithrombotic Trialists’ Collaboration, 2002

Absolute effects on vascular events in various high-risk groups

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>Benefit per 1000(SE)</th>
<th>Average duration</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A = Antiplatelet therapy</td>
<td>13.5% 17.0%</td>
<td>27 m</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>C = Control</td>
<td>10.4% 14.2%</td>
<td>1.3 m</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>A = Antiplatelet therapy</td>
<td>17.8% 21.4%</td>
<td>36(6)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>C = Control</td>
<td>8.1% 9.0%</td>
<td>29 m</td>
<td>0.002</td>
</tr>
<tr>
<td>A = Antiplatelet therapy</td>
<td>8.0% 10.2%</td>
<td>9(3)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>C = Control</td>
<td>9.0% 10.2%</td>
<td>22 m</td>
<td>&lt;0.00001</td>
</tr>
</tbody>
</table>

Effect of aspirin on risk of recurrent stroke after TIA or non-disabling stroke

Algra A. J van Gijn. **Aspirin at any dose above 30mg offers only modest protection after cerebral ischaemia.** JNNP 1996; 60: 197-99.

10 RCTs

Outcome: Stroke, MI, vasc.death

**Relative risk reduction = 13% (4-21)**

High-dose: 14% (2-24)

Medium-dose: 9% (-9-24) ns

Low-dose: 13% (-3-27) ns
Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials

Peter M Rothwell, Ale Algra, Zhengming Chen, Hans-Christoph Diener, Bo Norrvig, Ziyah Mehta

Lancet 2016 May 18th (online)

Risk of recurrent stroke during early follow-up in 12 trials of aspirin vs control in after a recent TIA/stroke

- Aspirin only
- Control

0-6 weeks
- Disabling or fatal ischaemic stroke
- Ischaemic stroke

P<0.0001

6-12 weeks

P=0.85

>12 weeks
Effect of aspirin vs control on the severity (mRS on follow-up) of recurrent ischaemic strokes in the first 6 and 12 weeks after randomisation in trials in secondary prevention after TIA and ischaemic stroke.
Pooled analysis of the early risk of recurrent stroke in 12 trials of any aspirin vs control in secondary prevention after a recent TIA and ischaemic stroke

Patients with TIA and minor stroke only

Disabling ischaemic stroke

0-2 weeks: HR=0.07, 0.02-0.31, p=0.0004
0-6 weeks: HR=0.19, 0.11-0.34, p<0.0001
0-12 weeks: HR=0.27, 0.17-0.41, p<0.0001

Disabling ischaemic stroke and acute MI

0-2 weeks: HR=0.11, 0.04-0.31, p<0.0001
0-6 weeks: HR=0.19, 0.11-0.31, P<0.0001
0-12 weeks: HR=0.27, 0.19-0.39, P<0.0001

All patients

Disabling ischaemic stroke

0-2 weeks: HR=0.36, 0.20-0.64, p=0.0005
0-6 weeks: HR=0.29, 0.19-0.46, p<0.0001
0-12 weeks: HR=0.35, 0.26-0.47, p<0.0001

Disabling ischaemic stroke and acute MI

0-2 weeks: HR=0.32, 0.19-0.54, P<0.0001
0-6 weeks: HR=0.27, 0.19-0.39, P<0.0001
0-12 weeks: HR=0.34, 0.26-0.44, P<0.0001

Lancet 2016 May 18th
Prospective Studies Collaboration

Consistent results from trials of BP-lowering in secondary prevention after TIA/stroke
Variation in BP – baseline vs first follow-up

Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension

Peter M Rothwell, Sally C Howard, Eamon Dolan, Eoin O'Brien, Joanna E Dobson, Bjorn Dahlof, Peter S Sever, Neil R Poulter

Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis

Alistair J Webb, Lin Fischer, Ziyaal Mehta, Peter M Rothwell

Effects of β blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke

Peter M Rothwell, Sally C Howard, Eamon Dolan, Eoin O'Brien, Joanna E Dobson, Bjorn Dahlof, Neil R Poulter, Peter S Sever, on behalf of the ASCOT-BPLA and MRCTriat Investigators

Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension

Peter M Rothwell
BPLTC pooled analysis of 28 trials: Risk of stroke and CV events vs mean and range of SBP

Hazard ratio

Mean systolic blood pressure

- - - - Range < 20  - - - - Range 20-39  - - - - Range 40+

Unpublished data
OXVASC
Bluetooth
Home BP monitoring

COMMIT Study
- 1200 patients
- 2886 drug changes
- 92% uptake
Predictive value for all cardiovascular events of residual hypertension based on home telemetric BP-monitoring versus 24 hour ambulatory monitoring monitoring (COMMIT Study)

Hypertension on home monitoring

Hypertension on 24-hour ABPM

Unpublished data
Effect of treatment on variability in SBP in ASCOT-BPLA

Lancet Neurol 2010; 9: 469-80
Pooled estimates of VR in parallel group trials in BPLTC: Intra-individual versus inter-individual variability

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<th>Drug class vs all other drug classes or placebo</th>
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Unpublished data

Variance Ratio (95% CI)
Spectrum of medical research

Clinical innovation

Clinical effectiveness

Clinical exploration

Basic laboratory science

“Translational research”

Cohort studies

Randomized trials

Population studies

Clinical practice
First ever synthetic pharmaceutical

• 1897 – August 10th – first sample prepared by Felix Hoffman - tries it out on colleagues & family – great for rheumatism

• A- Acetylation, SPIR – Spiraea ulmaria (meadowsweet), IN (ending for all drug names)

• 1899 – Bayer releases acetyl-salicylic acid in a powder form for medicinal purposes, credits Hoffman with the discovery.

• 1853 – French Chemist, Charles Frederich Gerhardt combined sodium salicylate and acetyl chloride to get acetyl-salicylic acid (ASA).
Arachidonic Acid

\[ \text{COX-1} \]
\[ \text{COX-2} \]
\[ \text{PGH}_2 \]
Prostaglandin synthases
\[ \text{PGD}_2, \text{PGF}_{2\alpha}, \text{PGI}_2, \text{TXA}_2 \]
\[ \text{PGE}_2 \]
\[ \text{EP1, EP2, EP3, EP4} \]

Prostanoids:

Prostaglandin \( E_2 \) receptors:

PPAR\( \delta \)  \( \beta \)-Catenin  EGF-R  PI3K/AKT

Target genes:

Cyclin D1  Bcl-2  VEGF

Effect:

Growth  Migration & invasion  Anti-apoptosis  Angiogenesis

Modified from Markowitz. NEJM 2007;356:2195-8
Risk of death due to cancer during **20-year follow-up** of three RCTs of aspirin versus control: 12,659 patients; 1364 cancer deaths.
Effect of aspirin on risk of colorectal cancer in relation to dose, frequency and duration, baseline characteristics, and tumour site: long-term follow-up of 80,000 subjects from randomised trials

Unpublished data
Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial

Wendy S Atkin, Rob Edwards, Ines Kraij-Hans, Kate Wooldrage, Andrew R Hart, John M A Northover, D Max Parkin, Jane Wardle, Stephen W Duffy, Jack Cuzick, UK Flexible Sigmoidoscopy Trial Investigators

![Graph C: Distal colorectal cancer](image)

![Graph E: Proximal colon cancer](image)

Distal colorectal cancer

Proximal colon cancer
Effect of aspirin on risk of distant metastasis by site of metastasis: time from randomisation to presentation of metastasis

- **Lung metastasis**
- **Liver metastasis**
- **Brain metastasis**
- **Multiple metastasis**

Lancet 2012; 379:1591-601
**Add-Aspirin Trial:** 4 PHASE III TRIALS - OVERARCHING PROTOCOL

Participants undergone primary treatment with curative intent for an early stage common solid tumour

**RUN IN PERIOD** – 8 weeks Aspirin 100mg daily

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**COLORECTAL**
Stage II or stage III adenocarcinoma of the colon or rectum

**RANDOMISE**
- PLACEBO
- 100mg ASPIRIN
- 300mg ASPIRIN

**Primary Outcome:**
Disease-free survival

2600 participants

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**BREAST**
Node positive or high risk node negative invasive breast cancer

**RANDOMISE**
- PLACEBO
- 100mg ASPIRIN
- 300mg ASPIRIN

**Primary Outcome:**
Disease-free survival

3100 participants

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**GASTRO-OESOPHAGEAL**
Adenocarcinoma or squamous, oesophagus, OG J or stomach

**RANDOMISE**
- PLACEBO
- 100mg ASPIRIN
- 300mg ASPIRIN

**Primary Outcome:**
Overall survival

2100 participants

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**PROSTATE**
Post surgery or radical RT, intermediate to high risk (D'Amico)

**RANDOMISE**
- PLACEBO
- 100mg ASPIRIN
- 300mg ASPIRIN

**Primary Outcome:**
Biochemical RFS

2120 participants

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**FOLLOW-UP**

≥ 5 years, including active f/up largely aligned with standard care, and long term passive f/up through NCIN
Spectrum of medical research

Clinical innovation
Clinical effectiveness
Clinical exploration

Basic laboratory science
“Translational research”
Cohort studies
Randomized trials
Population studies
Clinical practice